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Racial Disparities in COVID-19 Severity are Partially Mediated by Chronic Stress– Evidence from a Large Integrated Healthcare System

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B.S. in Biology- Cellular and Molecular

Trinity University

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Abstract

Racial Disparities in COVID-19 Severity are Partially Mediated by Chronic Stress– Evidence from a Large Integrated Healthcare System

By Miranda Marie Montoya

Background: Chronic stress is disproportionally experienced by racial and ethnic minorities. Minorities have also experienced a disproportionate burden of severe COVID-19. Whether chronic stress explains the excess COVID-19 severity risk among racial minorities is unknown.

Methods: We included adults (≥18 years) enrolled in care at Kaiser Permanente Georgia (KPGA) with a confirmed COVID-19 diagnosis (defined by ICD-10 codes or positive PCR), from January 1, 2020 through September 30, 2021 (n=29,162), excluding those with incomplete biomarker data (n=18,096; 62.1%) for a final sample size of 11,066 participants. Self-reported race (Black, White, or Other) was defined using electronic medical record (EMR) data. Chronic stress, characterized as allostatic load (AL) score, was calculated based on 7 cardio-metabolic biomarkers extracted from KPGA's EMR at least 45 days prior to COVID-19 diagnosis, and defined as high, medium, or low. Severe COVID-19 was defined as hospitalization or mortality within 30 days of COVID-19 diagnosis. To assess if AL mediated the relationship between race and severe COVID-19, we used the Baron and Kenny method of mediation, using ordinal logistic regression analyses adjusted for age, sex, comorbidities, and neighborhood-level socioeconomic factors.

Results: Among 11,066 adult KPGA members with COVID-19 and complete biomarkers, 26%, 58%, and 16%, had low, moderate, and high AL, respectively. Black (vs. White) KPGA members were 56% (OR: 1.56, 95%CI: 1.40,1.74) more likely to have moderate AL and 30% (OR: 1.30, 95%CI: 1.14,1.49) more likely to have severe COVID-19. Other (vs. White) members were 20% (OR: 1.20, 95%CI: 1.04,1.39) more likely to have moderate AL and equally likely (OR: 1.05, 95%CI: 0.86,1.28) to have severe COVID-19. Adjustment for AL risk in fully adjusted models showed that partial mediation by AL risk explained 18.0% of the disparity in severe COVID-19 among Black vs. white populations, while there was no evidence of AL mediation in Other vs. white populations.

Conclusion: In our study, chronic stress partially mediates the relationship between race and COVID-19 severity. To mitigate excess COVID-19 risk, future interventions should target systematic and structural factors that increase stress, including racial discrimination, housing standards and accessibility, an equitable living wage, and access to affordable healthcare.

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Literature Review

Overview

Racial disparities in health have long been reported, particularly in life expectancy, burden of chronic health conditions, and mortality (1,2). The COVID-19 pandemic highlighted these longstanding health disparities with minority populations facing the greatest burden of COVID-19 cases and the highest mortality rates from COVID-19 (2–4). This disparity, can be explained, in part, by differences in structural factors such as housing density, frontline worker demographics, and access to health care (1,2). However, differences in socioeconomic factors by race do not explain all of the observed disparities. For example, research has shown that Black communities faced higher mortality rates at all socioeconomic status levels, when compared to primarily White communities, suggesting there are other factors at play (5,6). While there is a general understanding that structural racism plays a role in maintaining these health gaps, there is little knowledge on the causal mechanisms resulting in these poor health outcomes.

The weathering hypothesis, developed in the 1990s, states that chronic exposure to social and economic disadvantage over the life course can lead to rapid health declines and, in turn, may play a role in upholding persistent racial disparities in health outcomes (7,8). It posits, therefore, that chronic stress may explain some of the observed racial disparities in COVID-19 outcomes. In this review, I summarize the current evidence regarding race and COVID-19 outcomes, and the potential role of stress in explaining the excess burden of COVID-19 among minority populations.

The Epidemiology of Race and COVID-19

The COVID-19 pandemic has been an ongoing health crisis since January 2020 (2). According to data from the Centers for Disease Control, in the US, there has been over 103 million total cases, as of March 2023, with about 1.1 million (1.1%) of them resulting in death (9). Compared to other similarly large and wealthy countries, the US experienced the highest rate of mortality among people under age 65, and this may be attributed, at least in part, to ongoing structural failures and systemic racism (10,11). According to analyses done by Hill and Artiga (12), "Black, Hispanic, and American Indian/Alaskan Native (AIAN) and Native Hawaiian and other Pacific Islander (NHOPI) people experienced higher rates of COVID-19 infection and death compared to White people, even after accounting for age differences across racial and ethnic groups". When comparing cumulative mortality rate, Hispanic, AIAN, and Native Hawaiian and other Pacific Islander populations experienced nearly double the mortality rate when compared to White populations, such that White people experienced a mortality rate of 268.5 deaths per 100,000 people, while minority populations experienced a mortality rate of 441.9, 466, 552.4, and 463.7 per 100,000 people, respectively in Hispanic, AIAN, and Native Hawaiian and other Pacific Islander populations(**Figure 1**) (4). Additionally, data shows that severe COVID-19 illness, as measured by hospitalization. For example, non-Hispanic, AIAN, Black or African American, and Hispanic individuals, were 2.7, 2.3, 2.0 times, respectively, more likely to be hospitalized with COVID-19, when compared to their White counterparts (2,3).

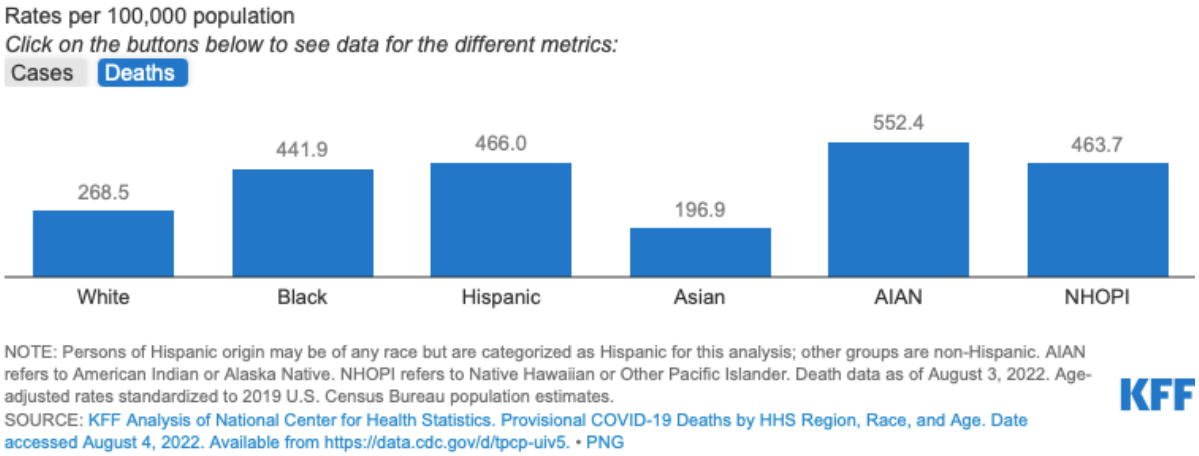

Figure 1. *Cumulative COVID-19 Age-Adjusted Mortality Rates by Race/Ethnicity, 2020-2022*. Extracted from Hill and Artiga (4).

Race and Stress

There is no single definition of stress (13,14). In 2018, Del Giudice et al. attempted to derive a definition of stress, applicable across multiple subjects and biological levels, which states that "stress occurs when a biological control system detects a failure to control a fitness-critical variable" (13). Essentially this means that when an environmental stimulus is perceived by an individual as a threat or problem, their biological systems are triggered to respond (15). Thus, it posits that stress is a state of threatened homeostasis provoked by a psychological, environmental, or physiological stressor (16,17). Stress can be further defined depending on the intensity and repetitiveness of stressors. Acute stress is most often used to describe short and sudden stressors lower in severity, while chronic stress is typically used to describe more robust and repetitive stressors, which tend to be more major stressful life events (5,15). In the biomedical literature, one way to define and measure stress is via allostatic load (AL). AL was conceived by McEwen (18) and is summarized as "the wear and tear on the body and brain

resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge". More directly, AL is a biomarker-based indicator of the cumulative, multilevel physiological response to chronic stress (**Table 1**) (5,17,19–25).

Table 1: Relative frequency of biomarkers of allostatic load by system. Adapted from Rodriguez et al (5).

Frequency	Cardiovascular System	Metabolic System	Inflammatory System
Most frequent	Systolic blood pressure	Glycated hemoglobin	C-reactive protein
	Diastolic blood pressure	Waist-hip ratio	Interleukin-6
	Total cholesterol	Body mass index	Fibrinogen
Moderately Frequent	HDL cholesterol	Albumin	Insulin-like growth factor-1
	Triglycerides*	Fasting glucose, plasma	Tumor necrosis factor alpha
	Heart rate	Waist circumference	Interleukin-10
	Homocysteine	Estimated GFR	Herpes simplex
Least frequent	FEV_1/FVC**	2-hour glucose	Interleukin-1
	Pulse pressure	LDL cholesterol	
		HOMA-IR	
		Apolipoprotein A1	
		Apolipoprotein B	

FEV_1/FVC[b] ratio of forced expiratory volume in 1 second to forced vital capacity, *GFR* glomerular filtration rate, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model assessment of insulin resistance, *LDL* low-density lipoprotein

* Triglycerides have been suggested to not be routinely included in the measurement of allostatic African Americans
** FEV_1/FVC is included in the cardiovascular system because of its use as a marker of cardiopulmonary function

Research has found that there are disparities in stress exposure across race, such that results show that U.S. and foreign-born Hispanic and Black individuals are more likely to report more chronic stress exposure than White individuals (26,27). The Weathering hypothesis, developed in the 1990s, states that chronic exposure to social and economic disadvantage leads to a rapid health decline and may play a role in upholding persistent racial disparities (7,8) Additionally, Cundiff et al. (28), reported that "Black Americans with lower income and

education reported greater psychological stress and may be at higher risk for disease through stress-related pathways", suggesting that differences across race may intersect with socioeconomic status (SES). These findings are echoed existing research on AL, such that disparities exist in average AL across race, SES, and gender (5,21,24). Differences across race and SES are intersectional. For example, a study of 518 older Black and White adults found that racial disparities in AL were dependent on an individual's lifetime SES [i.e. changes in SES from childhood to adulthood] (6). Additionally, it is important to note that disparities in AL across SES are strong and apparent among, both, African American and White populations (5,21,24). However, there are few studies dedicated to examining AL in the context of race and health outcomes, and to date it has not been studied in the setting of COVID-19.

The Stress-Health Mechanistic Pathway

The theory of allostasis suggests that AL may be used as a marker of overall physiological health and may explain the connection between chronic stress and health (23). According to a review of literature on Weathering, Forde et. al. (7) found that studies on "allostatic load have provided biological and physiological evidence of the weathering hypothesis", however the pathway in which this occurs and how chronic stress fits in to it is still being studied. The model in **Figure 2** is currently the most expanded transdisciplinary model of stress, depicting how contextual factors, cumulative stress, and protective factors interact to impact biological aging and development of early disease. In this model, the pathway to poor health is cyclical in nature and starts with early changes in stress hormones and anti-inflammatory cytokines in response to an initial stress stimulus. According to this pathway, chronic stress results in consistent activation of the pathway, such that adaption is accelerated,

and response systems become worn down as a result of overactivity (16,18,26). This adaptation and wearing down is ultimately what results in poor health outcomes, in that normal bodily responses are suppressed, impairing its ability to respond to future stressors or threats (14,16,19).

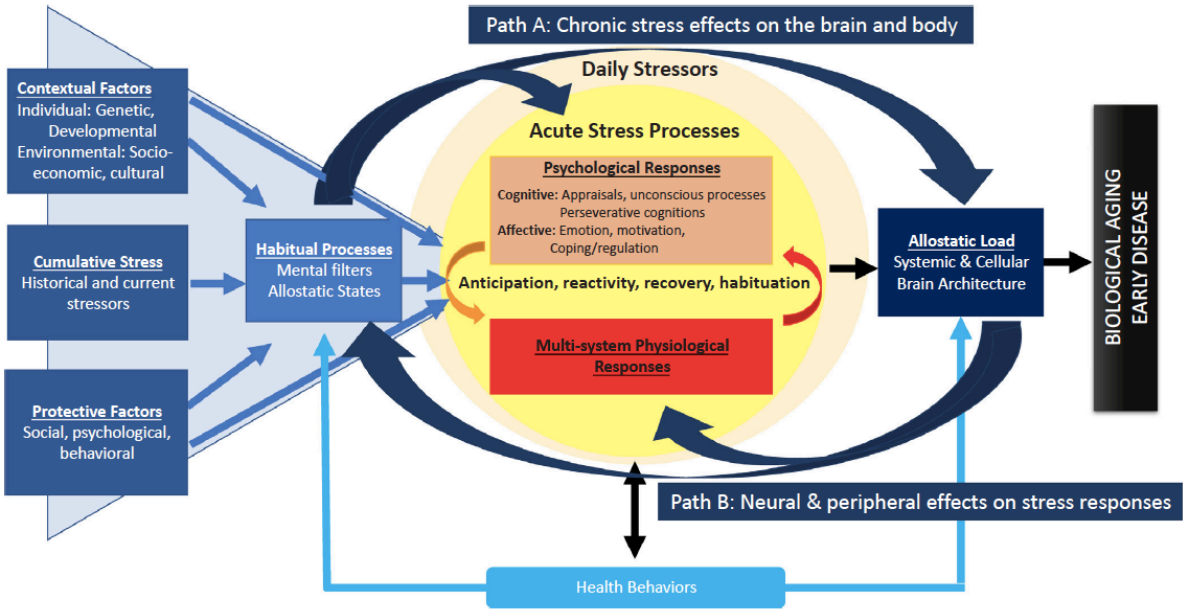

Figure 2. *Transdisciplinary model of stress: Integrating contextual, historical, habitual, and acute stress processes.* Extracted from Epel et. al. (14).

Despite the automatic and biological nature of this pathway, it is important to note some of the intervening contextual and protective factors in this model that can be acted upon to improve outcomes. Additionally, some studies have suggested that health-promoting behaviors act as a protective factor, in that physical activity and healthy coping mechanisms can reduce the effects of stress on bodily systems (15,29). Research has posited that the physical consequence of socioeconomic disadvantage, as measured by stress and poverty levels, vary across race, such that US-born Hispanics and Black individuals reporting more chronic stressors are less affected

by individual stressors, suggesting differences in stress-appraisal and the health effects of stress (27). These findings hint at a dynamic relationship between SES and the effects of stress on health. One interesting caveat to the transdisciplinary model of stress (**Figure 2**) is that although many experiences can be seen as stressful, not all are enough to produce an allostatic response, such that activation of this pathway may be dose-dependent or subject to and individuals' perception of the stressor (19,29).

Stress and Health Outcomes

Stress is a common risk factor for many diseases, such that 75-90% of diseases are thought to be stress-related (16). Physiological wear and tear, measured by AL, is associated with an increased risk of disease and early death (14,23,30). To date, evidence exists to suggest that chronic stress significantly increases the risk of depression, metabolic, and cardiovascular disease (CVD) (15,16,26,28). Research also suggests a dose relationship with a greater number of stressful events or high perceived stress over longer periods of time associated with worse mental and physical health, and overall mortality (15,26). More specifically, those with higher stress are at an increased risk of CVDs, metabolic diseases, and psychotic and neurodegenerative disorders (16,20,23,28). For example, a cross-sectional study of 26,451 adults 45 years and above found that high levels of perceived stress were associated with an increased risk of atrial fibrillation (OR = 1.60, 95%CI 1.39 to 1.84) (28). Evidence suggests that AL may not be useful as a predictor for cause-specific mortality, however, some studies have found evidence for its use as a predictor of all-cause mortality (23). For example, in a study of 4,488 men and women, "higher AL was not associated with an increased risk of all-cause mortality after 5 years (HR =1.07, 95% CI 0.94 to 1.22; p = 0.269), but it was after 10 years (HR = 1.08, 95% CI 1.01 to

1.16; p = 0.026)" (23), suggesting that it is the cumulative nature of stress over time that impacts health. Additionally, in a study of 1,189 men and women "higher allostatic load explained 35% of the difference in mortality risk between those of higher SES and those of lower SES… [and] higher SES predicted lower allostatic load" (24).

Brown et. al. (27) summarized racial disparities in stress-related diseases through the differential exposure hypothesis, which states that racial and ethnic minority groups are at an increases risk of poor heath as a result of increased exposure to stress throughout their lifetime, when compared to their White counterparts. Studies on this relationship have supported the differential exposure hypothesis, in that "inflammation arising from cumulative exposure to stress placed Black men at a greater risk for developing diabetes and cardiovascular disease than White men" (7,16). These finding also intersect across SES and gender, such that individuals falling into multiple minority categories may be at an increased risk of disease (28,31). For example, in a cohort study of 26,451 Black and White US adults 45 years and above, it was found that Black Americans, particularly those with a lower SES reporting greater psychological stress, were at an increased risk of diseases through the stress pathway, including stroke and other cardiovascular diseases (28). Additionally, they found that the effects of discrimination on health were significantly larger in Black women when compared to Black men (8). To date, limited data reports on the effects of cumulative stress on the incidence of infectious disease, including COVID-19; however, recent publications have suggested that contextual and environmental factors, such as SES, access to healthcare, and racism, are predictive of COVID-19 cases and outcomes, suggesting that chronic stress may too be a risk factor for severe COVID-19 outcomes (2,30).

Conclusion

Racial and ethnic minorities are at an increased risk of severe COVID-19 outcomes, including hospitalization and mortality. Given that race is associated with stress, and that stress in turn is associated with several health outcomes, it is plausible that stress may mediate the relationship between race and severe COVID-19. Yet, to date, there are no studies on the effects of cumulative stress on race and severity of COVID-19. To reduce racial health disparities in COVID-19, and possibly other infectious diseases, we must understand the role chronic stress plays in mediating this relationship, potentially revealing opportunities for intervention.

Introduction

Racial disparities in health have long been reported, particularly in life expectancy, burden of chronic health conditions, and mortality (1,2). The COVID-19 pandemic highlighted these longstanding health disparities with minority populations facing the greatest burden of COVID-19 cases and the highest mortality rates from COVID-19 (2–4). This disparity, can be explained, in part, by differences in structural factors such as housing density, frontline worker demographics, and access to health care (1,2). While there is a general understanding that structural racism plays a role in maintaining these health gaps, there is little knowledge on the mechanisms resulting in these poor health outcomes. The Weathering Hypothesis, developed in the 1990s, states that chronic exposure to social and economic disadvantage leads to a rapid health decline and may play a role in upholding persistent racial disparities (7,8) with foreign-born Hispanic and Black individuals more likely to report more chronic stress exposure than White individuals (26,27).

Stress, as measured often by AL, a physiological measure of wear and tear calculated by scoring biomarkers based on their risk categorization, is associated with an increased risk of disease, including depression, metabolic and cardiovascular diseases, early death and some infections (14–16,23,26,28,30). Evidence also shows that stress is different in different race groups with racial and ethnic minority groups are at an increased risk of poor heath as a result of increased exposure to stress throughout their lifetime. To date, research has only revealed that increased stress exposure places an individual at a higher risk of infection, but this relationship has not yet been substantiated in analytical studies, and there are no studies assessing cumulative stress as a mediator of race and COVID-19 severity.

Study Aims

In this study, we will explore whether chronic stress exposure, as measured by AL, mediates the relationship between race and COVID-19 severity (i.e., hospitalization and mortality).

Methods

Study Population

Data for this study was derived from the electronic medical records (EMR) of members of Kaiser Permanente Georgia's (KPGA) integrated healthcare system who were diagnosed with COVID-19 between Jan 1, 2020 and September 30, 2021 (n=31,500). COVID-19 was defined by a positive COVID-19 PCR test or an ICD-10 diagnosis (code U07.1, B97.29, B34.2, B97.21, or J12.81). We excluded anyone who was <18 at time of COVID-19 diagnosis (n=2,337), or missing data on gender, age, or race (n=1), or any of the biomarkers of interest (n=18,096; 62.1%), **Figure 3**. Individuals with missing biomarker data were more likely to be non-Black

racial minorities, younger, men, and have fewer pre-existing comorbidities, compared to those with complete biomarker data (**Table S1**). Our final sample included 11,066 adults with COVID-19 and measured biomarker data.

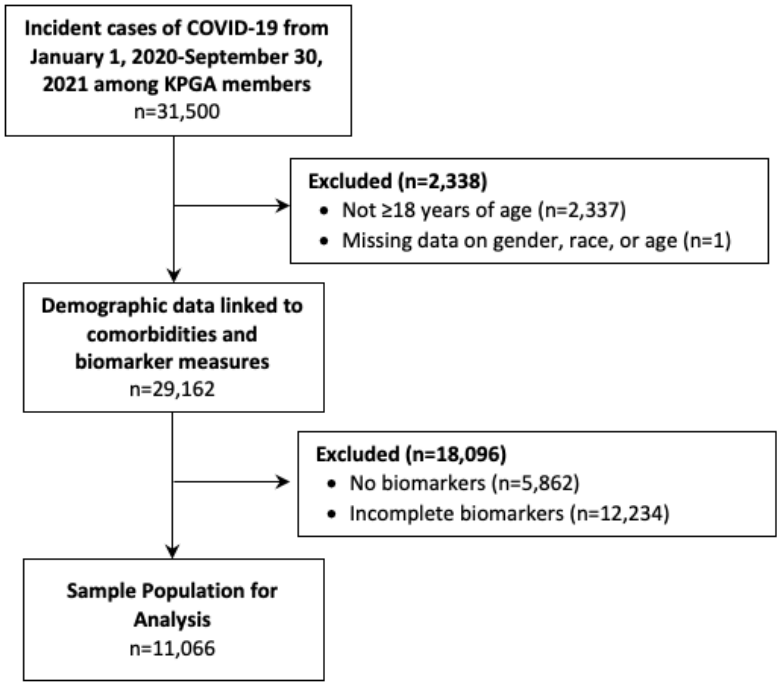

Figure 3. *CONSORT Diagram for CURE Study Understanding Race, Chronic Stress, and Severe COVID-19 among KGPA Members*

Race

Race is social construct that is used to categorize groups based on their physical and cultural features, and comes with an implicit meaning attached to it that impacts lived experiences, such as one's economic and social environments (2,32). Thus, the use of race as an exposure is a proxy for the level structural racism experienced to those historically marginalized (33). We defined individuals as Black, White, or Other based on self-reported race detailed in the

EMR and ethnicity was not considered. The Other category included those identifying as Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, Multiple races, and others [defined as those who did not identify as any of the race options]. For individuals with missing race, n=1,194 (10.79%), we imputed race using a probability distribution developed from RAND's Bayesian Improved Surname and Geocoding (BISG) algorithm using patient zip code and surname (34). This BISG method of imputation was found to be 41% more effective than methods using only surnames and 108% more effective than those only using zip code, and have a predictive accuracy of 93% for both Black and White individuals (35).

Chronic Stress: Allostatic Load Construction

Chronic stress was measured using AL and calculated based on seven cardio-metabolite biomarkers. These biomarkers were measured within 45 days and up to five years before the first COVID-19 diagnosis. Each biomarker was given a score: 1 for high-risk, 0.5 for moderate risk, and 0 for low risk, based on current clinical guidelines (**Table 2**). For albumin and creatinine, current guidelines are limited to high- or low-risk and thus no moderate score was given for these biomarkers. Data on blood pressure was not collected, so a history of anti-hypertensive medication was used as a proxy for high blood pressure (see **appendix A**). These scores were then summed to determine a total AL score, on a scale of 0-7 (5,21,22), and categorized as low- (score 0-1.5), moderate- (2-3.5), or high-risk (≥4).

Table 2. Clinically Relevant Biomarker Cutoffs

System	Measures	AL Risk Categorization	Clinical Cut Off	Source
Cardiovascular	Total cholesterol	High (score 1)	≥240 mg/dL	National Cholesterol Education Program (36)
		Medium (score 0.5)	200 - <240 mg/dL	
		Low (score 0)	<200 mg/dL	
	HDL cholesterol	High (score 1)	<40 mg/dL	National Cholesterol Education Program (36)
		Medium (score 0.5)	40 - <60 mg/dL	
		Low (score 0)	≥60 mg/dL	
	Blood pressure*	High (score 1)	Taking blood pressure meds	Prescriber's Digital Reference (37)
		Low (score 0)	No reported meds	
Metabolic	Glycated hemoglobin	High (score 1)	≥6.5 %	American Diabetes Association (38)
		Medium (score 0.5)	5.7 - <6.5%	
		Low (score 0)	<5.7 %	
	Body mass index	High (score 1)	<18 kg/m2; ≥30 kg/m2	Center for Disease Control (39)
		Medium (score 0.5)	25 - <30 kg/m2	
		Low (score 0)	18 - <25 kg/m2	
	Albumin*	High (score 1)	Outside normal range	Clinical Key (40)
		Low (score 0)	Normal range: 3.5 - 5.5 g/dL	
	Creatinine*	High (score 1)	Outside normal range	Medline Plus Medical Text (41)
		Low (score 0)	Normal range: 0.65 - 1.2 mg/dL	

*Denotes the absence of a moderate risk categorization

Severe COVID-19

COVID-19 severity was defined as hospitalization or mortality within 30 days of COVID-19 diagnosis. Due to the limited number of deaths in this population, the decision was made to combine hospitalizations and mortality in the definition of severe COVID-19.

Covariates

Using KPGA EMR, we included data on age, sex, and high deductible insurance plan (yes/no) at time of COVID-19 diagnoses. Quartiles of the Center for Disease Control Social Vulnerability Index (CDC SVI) (42) and median household income, was ascertained from the American Community Survey and were matched according to patient zip codes. Each comorbidity was coded binarily and marked yes for any report throughout the participant's entire history of enrollment with KPGA, or no if not reported. Smoking history was ascertained using ICD-10-CM and ICD-9-CM codes (see **Appendix B**). History of alcohol overuse, depression, chronic obstructive pulmonary disease (COPD), liver disease, renal disease, and coronary heart disease (CHD) were ascertained either from the Elixhauser Comorbidity Index (43) or the Charlson Comorbidity Index (44) and extracted from EMRs (45) according to ICD-9/10-CM codes (see **Appendix C**). **Figure 3** shows that only 1 individual was missing data on gender and was excluded. Less than 0.1% (n=7) of patients were missing data on socioeconomic measures including SVI, median household income, and insurance status. There was no missingness in smoking history, alcohol overuse, and comorbidities. Given the small amount of missing data in this EMR cohort, we conducted a complete case analysis.

Statistical Analysis

Baseline characteristics of the study population, by high, moderate, or low AL, were compared using t-tests for continuous variables and chi square for categorical variables. All continuous variables were normally distributed. To examine whether AL mediates the relationship between race and COVID-19 severity, we used the Barron and Kenny method of mediation analysis (**Figure 4**). Mediation was tested with three logistic regression analyses: 1) association between race and COVID-19 severity, 2) association between race and AL, and 3) association between race and COVID-19 severity, adjusted for AL. To account for several potential confounders, each regression utilized sequential models. In a first step, we estimated associations across all 3 regression analyses with only the exposure of interest and the AL mediator (Model 1). In a second step, we adjusted for potential confounders in a stepwise manner as follows: Model 2 adjusted for age and gender, Model 3 adjusted for Model 2 covariates and SVI, median household income, and insurance status, Model 4 adjusted for Model 3 covariates plus smoking status, alcohol use, and depression, Model 5 adjusted for Model 4 covariates plus COPD and liver disease, and Model 6 adjusted for Model 5 covariates plus renal disease and CHD. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). When assessing race and AL (**Relationship 2**), each ordinal logistic regression (OLR) underwent the proportional odds assumption Score Test. If the assumption was met, we proceeded with OLR and only one OR was reported, representative of the overall association between race and AL risk. However, if the assumption was not met, we proceeded with polytomous logistic regression (PLR) and strata specific ORs were reported, using the low AL risk as the reference. Mediation assessment involved the comparison of the ORs from the unadjusted (**Relationship 1**) to the AL risk-adjusted (**Relationship 3)** models, **Figure 4.** Percent

disparity attenuated (i.e., % of race-severe COVID-19 relationship explained by AL) was derived by calculating the percent change in OR estimations from the unadjusted association of race and severe COVID-19 to the AL-adjusted race and severe COVID-19 relationship, as a fraction of the change in OR estimation over the unadjusted estimation.

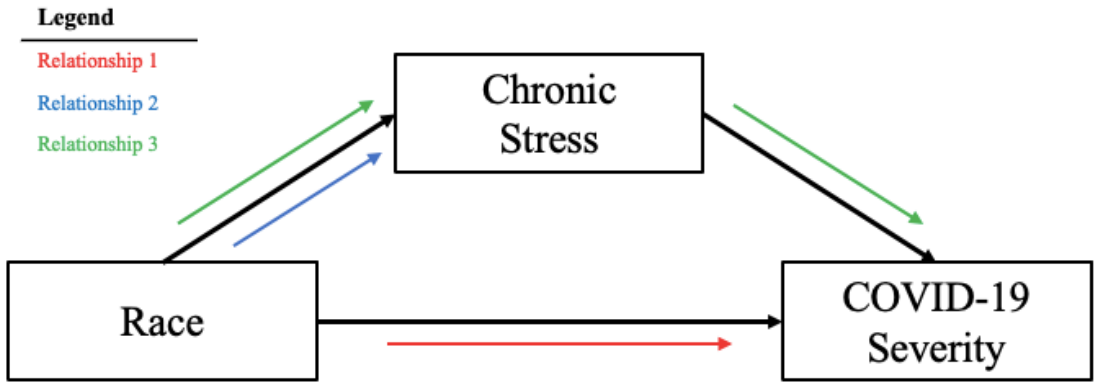

Figure 4. Directed Acyclic Graph of the Relationship Between Race, Chronic Stress, and COVID-19 Severity

Sensitivity Analyses

In sensitivity analyses, we defined AL as: 1) six cardio-metabolic biomarkers excluding BP, utilizing the cutoffs in **Table 2**, and 2) using sample-dependent quartiles as cutoffs for AL, **Table S2**. These AL definitions, in contract to our primary definition, are described in **Table 3**. Statistical analyses, as outlined above, was carried out for each new definition of AL.

All analyses were conducted via SAS v 9.4 (SAS Institute Inc.). Study ethics and research dissemination were reviewed and approved by The Kaiser Permanente Georgia Institutional Review Board (IRB# 00000406) and Emory University Institutional Review Board (IRB#: STUDY00001631).

Table 3. Methods of Allostatic Load Determination

Method # (analysis)	**Score Range**	**Scoring Method**
Method 1 (primary)	0-7	Scoring of 7 cardio-metabolite biomarkers, including total cholesterol, HDL cholesterol, glycated hemoglobin, BMI, albumin, creatinine, and a blood pressure proxy based on clinically relevant cutoffs (**Table 2**)
Method 2 (sensitivity)	0-6	Scoring of 6 cardio-metabolite biomarkers, including total cholesterol, HDL cholesterol, glycated hemoglobin, BMI, albumin, and creatinine based on clinically relevant cutoffs (**Table 2**)
Method 3 (sensitivity)	0-6	Scoring of 6 cardio-metabolite biomarkers, including total cholesterol, HDL cholesterol, glycated hemoglobin, BMI, albumin, and creatinine based on sample-dependent quartile cutoffs (**Table S2**)

Results

Baseline Characteristics

Among KPGA members with COVID-19 and measured biomarkers, 36.1% were White, 50.4% Black, and 13.5% were Other (where other is made up of Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, Multiple races, and others). Black KPGA members were more likely to be women, younger, live in a low-income neighborhood with higher social vulnerability, have a moderate to high AL risk level, and be diagnosed with COPD, CHD, and renal disease, but less likely to report a history of smoking or alcohol overuse as compared to White and Other members.

Overall, 25.9%, 58.3%, and 15.8% of the study population were considered to have high-, moderate-, and low-AL risk, respectively. People with moderate to high AL risk were more likely to be Black, men, older, live in a low-income neighborhood with higher social vulnerability, have a documented history of smoking, and be diagnosed with depression, COPD, liver disease, CHD, and renal disease, when compared to those with a low AL risk (**Table S3**).

Table 4. Sample Characteristics of adult KGPA Members with an Incident COVID-19 Diagnosis, 2020-2021, by Race

Sample Characteristics	Total Study Population n = 11,066	Race		
		Black (n = 5,578)	**White** (n = 3,999)	**Other** (n = 1,489)
Demographics				
Gender, n(%)				
Female	6774 (61)	3721 (67)	2223 (56)	830 (56)
Male	4292 (39)	1857 (33)	1776 (44)	659 (44)
Age, mean (SD)	52.19 (14.3)	50.63 (13.6)	55.18 (15.1)	49.97 (13.6)
Median Household Income, n(%)				
50k or less	2802 (25)	1989 (36)	497 (12)	316 (21)
>50k to 100k	7224 (65)	3395 (61)	2866 (72)	963 (65)
>100k to 150k	898 (8)	168 (3)	538 (13)	192 (13)
>150k	136 (1)	21 (<1)	98 (2)	17 (1)
Social Vulnerability Index,* n(%)				
Lowest	2743 (25)	714 (13)	1605 (40)	424 (28)
Moderately low	3346 (30)	1488 (27)	1396 (35)	462 (31)
Moderately high	2782 (25)	1830 (33)	643 (16)	309 (21)
Highest	2188 (20)	1541 (28)	354 (9)	293 (20)
High Deductible Insurance, n(%)	454 (4)	228 (4)	142 (4)	84 (6)
Allostatic Risk Level, n(%)				
Low	2871 (26)	1262 (23)	1168 (29)	441 (29)
Moderate	6450 (58)	3320 (59)	2270 (57)	860 (58)
High	1745 (16)	996 (18)	561 (14)	188 (13)
Comorbidities				
Smoking, n(%)	2074 (19)	916 (16)	1004 (25)	154 (10)
Alcohol Overuse, n(%)	525 (5)	255 (5)	237 (6)	33 (2)
Depression, n(%)	3333 (30)	1556 (28)	1475 (37)	302 (20)
COPD, n(%)	3768 (34)	1864 (33)	1520 (38)	384 (26)
Liver Disease, n(%)	179 (2)	74 (1)	81 (2)	24 (2)
Coronary Heart Disease, n(%)	853 (8)	451 (8)	356 (9)	46 (3)
Renal Disease, n(%)	1398 (13)	800 (14)	486 (12)	112 (8)

*CDC Social Vulnerability Index is reported on a scale of 0-1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest).

Race and Severe COVID-19

Overall, 14.7% (n=1,627) of our study population developed severe COVID-19, of which 88.1% (n=1,433) were hospitalized and 11.9% (n=194) died within 30 days of diagnosis. Overall, 15.61% (n=871), 14.8% (n=592), and 11.0% (n=164) of Black, White, and Other individuals, respectively, had severe COVID-19. In unadjusted models (model 1), Black KPGA members had a similar risk of severe COVID-19 (OR: 1.07, 95%CI: 0.95,1.19) while Other race groups had a lower risk (OR: 0.7, 95%CI: 0.59,0.86), as compared to White KPGA members **Table 5**. In fully adjusted models (Model 6), when compared to White KGPA members, Black individuals had a higher risk (OR: 1.30, 95%CI: 1.14,1.49) of severe COVID-19, while Other KGPA members had a similar risk (OR: 1.05, 95%CI: 0.86,1.28), **Table 5.**

Race and Allostatic Load

Overall, 22.6% (n=1,262), 29.2% (n=1,168), 29.6% (n=441) of Black, White, and Other KGPA members, respectively, had a low AL risk level, while 17.9% (n=996), 14.0% (n=561), 12.6% (n=188) of Black, White, and Other members, respectively, had a high AL risk level (**Table 4**). In unadjusted model (Model 1), Black individuals were more likely (OR: 1.38, 95%CI: 1.28, 1.50) to have a moderate to high AL risk, while Other individuals had a similar risk (OR: 0.95, 95%CI: 0.85, 1.07), as compared with White KPGA members, **Table 5.** In fully adjusted models (Model 6), Black KGPA members were more likely to have a moderate (OR: 1.56, 95%CI: 1.40, 1.74) and high AL (OR: 1.81, 95%CI: 1.55, 2.11) risk, compared to White KPGA members ,**Table 5**. Other KGPA members were more likely to have a moderate AL risk (OR: 1.20, 95%CI: 1.04, 1.39) and had a similar risk (OR: 1.19, 95%CI: 0.96, 1.47) of having a high AL risk, compared to White KGPA members, **Table 5**.

AL as a Mediator of Race and Severe COVID-19

When adjusting for AL risk in Model 1, Black individuals had a similar risk of severe COVID-19 (OR: 0.98, 95%CI:0.87, 1.10), while Other individuals had a lower risk (OR: 0.72, 95%CI: 0.60, 0.87) of severe COVID-19, compared to White KPGA members, **Table 5**. Adjustment for AL risk in the fully adjusted models (Model 6), showed that Black KGPA members had a higher risk of severe COVID-19 (OR: 1.24, 95%CI:1.08, 1.42), while Other members had a similar risk (OR: 1.04, 95%CI: 0.85, 1.27) of severe COVID-19, when compared to White KPGA members, **Table 5**. Fully adjusted models (Model 6) showed that partial mediation by AL risk explained 18.0% of the disparity in severe COVID-19 in Black population, while there was no evidence of mediation in Other populations, when compared to the White population.

Table 5. Odds Ratio Estimations[1] of the Meditation Relationships between Race, Allostatic Load, and COVID-19 Severity

Race	Model 1[2]	Model 2[3]	Model 3[4]	Model 4[5]	Model 5[6]	Model 6[7]
Relationship 1: Race and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	1.07 (0.95, 1.19)	**1.48 (1.31, 1.67)**	**1.32 (1.15, 1.50)**	**1.38 (1.21, 1.57)**	**1.39 (1.22, 1.60)**	**1.30 (1.14, 1.49)**
Other	**0.71 (0.59, 0.86)**	0.97 (0.80, 1.18)	0.93 (0.76, 1.13)	1.00 (0.82, 1.21)	1.01 (0.83, 1.24)	1.05 (0.86, 1.28)
Relationship 2: Race and Chronic Stress (Models 2-6 use "Low AL Risk" as reference)						
Moderate AL						
White, (ref)		--	--	--	--	--
Black		**1.71 (1.55, 1.89)**	**1.56 (1.40, 1.73)**	**1.59 (1.42, 1.77)**	**1.59 (1.43, 1.78)**	**1.56 (1.40, 1.74)**
Other	--	**1.21 (1.05, 1.39)**	**1.16 (1.01, 1.34)**	**1.19 (1.03, 1.37)**	**1.20 (1.05, 1.39)**	**1.20 (1.04, 1.39)**
	1.38 (1.28, 1.50)[8]					
High AL	0.95 (0.85, 1.07)[8]					
White, (ref)		--	--	--	--	--
Black		**2.46 (2.14, 2.83)**	**1.97 (1.70, 2.28)**	**2.07 (1.78, 2.41)**	**2.10 (1.81, 2.44)**	**1.81 (1.55, 2.11)**
Other		1.19 (0.97, 1.46)	1.08 (0.87, 1.33)	1.15 (0.93, 1.42)	1.17 (0.95, 1.45)	1.19 (0.96, 1.47)
Relationship 3: Race, Chronic Stress, and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	0.98 (0.87, 1.10)	**1.40 (1.18, 1.52)**	**1.22 (1.07, 1.39)**	**1.27 (1.11, 1.45)**	**1.29 (1.13, 1.48)**	**1.24 (1.08, 1.42)**
Other	**0.72 (0.60, 0.87)**	0.96 (0.79, 1.17)	0.93 (0.76, 1.13)	0.99 (0.82, 1.21)	1.01 (0.83, 1.23)	1.04 (0.85, 1.27)

[1] All reported measures are Odds Ratio (95% confidence intervals), using White as the reference group. Bolded estimates are significant.

[2] Model 1 only contains exposure of interest and the mediator, when applicable (Relationship 3)

[3] Model 2 adjusts for gender and age

[4] Model 3 adds CDC SVI, income, and high deductible insurance plan

[5] Model 4 adds smoking status, alcohol use, and depression

[6] Model 4 adds COPD and liver disease

[7] Model 6 adds renal disease and coronary heart disease

[8] Proportional odds assumption met for crude model, so OLR was performed and only one overall AL risk OR reported, representative of the odds of increased AL risk level, across race. Models 2-5 do not meet the assumption, so PLR regression was performed, and thus AL risk strata specific ORs are reported using "Low" allostatic load risk level as the reference group.

Sensitivity Analysis of Variations in Allostatic Load Score Determination

Using different AL definitions, the overall distributions of low, moderate, and high AL risk are different, **Table 6**. When utilizing Method 2 (i.e., 6 biomarkers, excluding BP), individuals with moderate to high AL risk were more likely to be Black race, men, older, live in a census tract with a median income less than $50,000 and a moderately high and above SVI, have a documented history of smoking, and be diagnosed with COPD and CHD, when compared to those with a low AL risk (**Table S4**). However, when utilizing Method 3 (6 biomarkers with quartile cutoffs), KGPA members with high AL risk were more likely to be of Black race, older, women, live in a census tract with a median income less than $50,000 and moderately high and above SVI, and be diagnosed with depression, COPD and CHD, when compared to those with a low to moderate AL risk (**Table S5**).

Table 6. Comparison of AL Risk Level Distributions Across Various AL Determination Methods

	Low, n (%)	**Moderate**, n (%)	**High**, n (%)
Method 1 (7 biomarkers)	2,871 (25.9)	6,450 (58.3)	1,745 (15.8)
Method 2 (6 biomarkers)	4,626 (41.8)	6,047 (54.6)	393 (3.6)
Method 3 (quartiles)	884 (8.0)	7,658 (69.2)	2,524 (22.8)

Overall, Method 2 (i.e., 6 biomarkers, excluding BP) results were similar to the original method (7 biomarkers) of AL determination with only changes in the magnitude of reported ORs (**Table S6**), while Method 3 (6 biomarkers with quartile cutoffs) results had significantly different results, both in the magnitude of ORs, primarily in the relationship between race and AL risk level, and differences in mediation results by race category (**Table S7**). When using

Method 2 (i.e., 6 biomarkers, excluding BP) of AL determination, declines in risk from the unadjusted to the AL risk-adjusted fully adjusted models, showed that partial mediation by AL risk explained 14.9% of the disparity in severe COVID-19 among Black KGPA members, while there was no evidence of mediation among Other KGPA members, compared to White KGPA members. However, the use of Method 3 (6 biomarkers with quartile cutoffs), showed no evidence of AL mediation among Black and Other KGPA members, compared to White KGPA members.

Discussion

In our study of KPGA members, chronic stress, as defined by AL, explained 18% of the excess risk of severe COVID-19 in Black vs. White KPGA members, but did not explain disparities between Other races and White KPGA members. Specifically, Black KPGA members were 30% more likely to have severe COVID-19, while Other KPGA members had a similar risk, when compared to White KPGA members. Thus, there was no observed disparity in COVID-19 severity among Other KGPA members. Compared to White individuals, Black individuals were 56% and 81% more likely to have a moderate and high AL risk, respectively. While Other individuals were 20% more likely to have a moderate AL risk, but equally likely to have a high AL risk, when compared to White individuals. Overall, results from this study suggest that chronic stress, may be an important target for future interventions to address the excess risk of severe COVID-19 experienced by some minority populations.

Our study is the first to examine AL as a mediator of the relationship between race and severe COVID-19. However, several non-COVID studies have examined the effects of AL mediation on other health outcomes with similar findings. For example, Duru et. al (47) found

that AL mediated Black-White disparities in cardiovascular and diabetes related mortality among women by 71.4%, but did not explain Black-White disparities among men. The sex-specific findings here are interesting and the authors suggest that these might be partially explained by genetic differences and psychological stressors, such as racism, health care accessibility and adverse financial incentives (47). The larger proportion of the relationship between race and diabetes/CVD being explained by AL may be due to the strong relationship each biomarker that makes up the AL score has with diabetes and CVD. For COVID-19, though there is some evidence that hyperglycemia and obesity may play a role (48,49) in increased risk for severe COVID-19, relationship with other biomarkers is less clear. It is also possible that for outcomes of diabetes and CVD, which take years to develop, chronic stress may a play a more important role than in something like severe COVID-19 with relatively acute onset.

Other studies have used other indices of socioeconomic status (SES), rather than race, to examine the role of AL on the risk of chronic disease. For example, one study found that 47.9% of the relationship between low SES and prevalent CKD was explained by AL, but AL did not explain SES disparities in incident CKD and declines in eGFR (50). These findings are relatively similar to ours as they constructed an AL score representative of multiple health systems and found that AL impacts health outcomes. However, similar to above, it is important to consider to what extent the relationship is explained by the biomarkers included in the AL score that are directly related to CKD, such as hyperglycemia and high blood pressure. In another study assessing the relationship between adverse childhood experiences (ACEs) and multimorbidity [defined as an index of 21 prevalent and high impact/burden conditions] they found that social engagement and AL acted as partial mediators (51). More specifically, they found that increases in ACEs are associated with an increased number of chronic conditions later in life

(multimorbidity), of which 28% and 23% of the association in females and males, respectively, was partially explained by the combined effects of AL and social engagement.

While decades of literature have revealed health disparities and identified systemic racism as a root cause, many fall short in identifying precise biological and social factors that may be impacting these outcomes. One potential mechanism to explain the connection between structural factors and health disparities is the Weathering Hypothesis, which suggests that chronic exposure to social and economic disadvantage leads to a rapid health decline and may play a role in upholding persistent racial disparities (7,8). Epel and colleagues have expanded upon this theory and have showed how contextual factors, cumulative stress, and protective factors interact to impact biological aging and early disease (14). In summary, they suggest the pathway to poor health is cyclical in nature and starts with early changes in stress hormones and anti-inflammatory cytokines in response to an initial stress stimulus. The theory of allostasis suggests that allostatic load may be used as a marker of overall physiological health and may explain the connection between chronic stress and health. The findings of our study support this hypothesis, such that the level of health impact in response to increased chronic stress exposures is determined by one's gender, race, socioeconomic background, and pre-existing health conditions. These findings imply that stress stemming from systemic issues have a negative impact on health.

It is likely that COVID-19 will become endemic with seasonal outbreaks, similar to the flu (52). Thus, the findings of our study have several important public health implications. First, our data suggest that reducing AL may reduce risk of severe COVID-19 in racial and ethnic minorities. This may include individualized care plans to reduce blood pressure, glucose, and BMI. However, we acknowledge that causes of high AL are likely upstream, such as ongoing

and systemic racism, and inadequate access to appropriate healthcare, housing, and financial support. Thus longer term solutions to mitigate excess risks for severe COVID-19 (and other chronic diseases) will likely include addressing factors such as racial discrimination, and improving housing standards and accessibility, moving towards an equitable living wage, and ensuring access to quality affordable healthcare should reduce the chronic stress levels universally (1,2,7,24,53).

The key strength of this study is the use of KPGA's expansive EMR system that allowed for a large sample size and clinically measured lab results, provider diagnosed comorbidities, and verified hospitalization and mortality information. A large sample size throughout the state of Georgia, which has a significantly larger Black population (33%) (54) compared to that of the US (13.6%) (55), resulted in our study having a large Black population, making this an ideal population to assess racial disparities. Furthermore, use of EMR data that is collected primarily for patient management, minimizes bias and the amount of missing data.

However, there are some limitations to consider. First, AL is a proxy for chronic stress, and there is no validated method to calculate AL despite some consistency across studies (5,21,24,56,57). We conducted sensitivity analyses altering our definition and showed sample-dependent quartile cutoffs (vs. guideline driven cut-offs) had different results, both in the magnitude of ORs and differences in mediation results. These findings disagree with the literature, which suggests that the quartile method tended to be robust, and even preferred in some cases (56,57). Further research should aim to conduct mixed-methods studies that can explore multiple measures of chronic stress, both qualitative and quantitative, allowing for a comparison of objective and subjective experiences.

Second, our results may not be generalizable to non-insured settings, or to individuals who do not have biomarkers routinely measured. Our study sample was restricted to individuals with available biomarker data. We show that, on average, those with biomarker data are more likely to be White, older, women, with a higher number of pre-existing comorbidities, compared to those with incomplete biomarker data. Nonetheless, we were able to examine the relationship between race, AL and severe COVID-19 among a group of people with relatively uniform access to healthcare via health insurance, the aim of this work. Third, our population has a higher proportion of Black individuals and thus may not be extrapolated to other populations or regions in the US. Fourth, our null findings for 'Other' race may be a type I error and due to limited sample size in this population. Future research should examine the impact of AL on severe COVID-19 in other ethnic and racial minorities. Fifth, AL is measured at baseline, and thus not a true mediator. Although AL biomarkers are taken at least 45 days prior to COVID-19 diagnosis, some can be up to 5 years pre-diagnosis, thus causality is not definitive. Further research should aim to conduct longitudinal studies with data collection at multiple timepoints, such that longer follow up periods with multiple measures will allow investigators to explore changes in chronic stress over time, providing a causal understanding. Finally, our study is limited to data captured in KPGA's EMR and thus likely has residual confounding as a result of missing data, in particular individual level SES variables.

Conclusion

In conclusion, in this study we show that Black members of an integrated healthcare system were at increased risk for developing severe COVID-19, and that this relationship is partially explained by chronic stress which is disparately experienced by minority populations. Future

research should aim to conduct longitudinal studies so that the causal pathway between AL and COVID-19 outcomes can be better understood. In the interim, management of the effects and number of social stressors and ensuring access to quality affordable healthcare may in part alleviate excess burden of COVID-19 in minority populations.

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Supplementary Tables

Table S1. Sample Characteristics of KPGA Members with an Incident COVID-19 Diagnosis by Levels of Biomarker Completeness

Sample Characteristics	Entire Study Population (n = 29,162)	Complete Biomarkers (n=11,066)	Incomplete Biomarkers (n=18,096)
Demographics			
Race, n(%)			
Black	14484 (50)	5578 (50)	8906 (49)
White	10028 (34)	3999 (36)	6029 (33)
Other	4650 (16)	1489 (14)	3161 (18)
Gender, n(%)			
Female	17102 (59)	6774 (61)	10328 (57)
Male	12060 (41)	4292 (39)	7768 (43)
Age, mean (SD)	45.25 (15.5)	52.19 (14.3)	41.01 (14.7)
Median Household Income, n(%)			
50k or less	7439 (26)	2802 (25)	4673 (26)
>50k to 100k	18625 (64)	7224 (65)	11401 (64)
>100k to 150k	2511 (9)	898 (8)	1613 (9)
>150k	384 (1)	136 (1)	248 (1)
Social Vulnerability Index,* n(%)			
Lowest	7457 (26)	2743 (25)	4714 (26)
Moderately low	8578 (30)	3346 (30)	5232 (29)
Moderately high	7928 (25)	2782 (25)	4526 (26)
Highest	5611 (19)	2188 (20)	3423 (19)
Comorbidities			
Smoking, n(%)	3530 (12)	2074 (19)	1456 (8)
Alcohol Overuse, n(%)	812 (3)	525 (5)	287 (2)
Depression, n(%)	5665 (19)	3333 (30)	2332 (13)
COPD, n(%)	6961 (24)	3768 (34)	3193 (18)
Liver Disease, n(%)	212 (1)	179 (2)	33 (0.2)
Coronary Heart Disease, n(%)	1088 (4)	853 (8)	235 (1)
Renal Disease, n(%)	1795 (6)	1398 (13)	397 (2)

*CDC Social Vulnerability Index is reported on a scale of 0-1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest).

Table S2. Biomarker Quartile Cutoffs

System	Measures	Health Risk Categorization	Clinical Cut Off
Cardiovascular	Total cholesterol	High (score 1)	≥206 mg/dL
		Medium (score 0.5)	154 - <206 mg/dL
		Low (score 0)	<154 mg/dL
	HDL cholesterol	High (score 1)	<41.7 mg/dL
		Medium (score 0.5)	41.7 - <60 mg/dL
		Low (score 0)	≥60 mg/dL
Metabolic	Glycated hemoglobin	High (score 1)	≥6 %
		Medium (score 0.5)	5.3 - <6%
		Low (score 0)	<5.3 %
	Body mass index	High (score 1)	<25.25 kg/m2; ≥35.4 kg/m2
		Medium (score 0.5)	29.83 - <35.4 kg/m2
		Low (score 0)	25.25 - <29.83 kg/m2
	Albumin	High (score 1)	<3.9 g/dL
		Medium (score 0.5)	3.9 - <4.4 g/dL
		Low (score 0)	≥4.4 g/dL
	Creatinine	High (score 1)	<0.8 mg/dL
		Medium (score 0.5)	0.8 - <1 mg/dL
		Low (score 0)	≥1 mg/dL

Table S3. Sample Characteristics of adult KGPA Members with an Incident COVID-19 Diagnosis, 2020-2021, by AL Risk Level

Sample Characteristics	Total Study Population	Allostatic Load Risk Level		
		High	**Moderate**	**Low**
	n = 11,066	(n = 1,745)	(n = 6,450)	(n = 2,871)
Demographics				
Race, n(%)				
Black	5578 (50)	996 (57)	3320 (52)	1262 (44)
White	3999 (36)	561 (32)	2270 (35)	1168 (41)
Other	1489 (14)	188 (11)	860 (13)	441 (15)
Gender, n(%)				
Female	6774 (61)	838 (48)	3926 (61)	2010 (70)
Male	4292 (39)	907 (52)	2524 (39)	861 (30)
Age, mean (SD)	52.19 (14.3)	56.88 (12.6)	53.55 (13.8)	46.27 (14.6)
Median Household Income, n(%)				
50k or less	2802 (25)	553 (32)	1644 (26)	605 (21)
>50k to 100k	7224 (65)	1076 (61)	4216 (65)	1932 (67)
>100k to 150k	898 (8)	101 (6)	515 (8)	282 (10)
>150k	136 (1)	15 (1)	70 (1)	51 (2)
Social Vulnerability Index,* n(%)				
Lowest	2743 (25)	339 (19)	1545 (24)	859 (30)
Moderately low	3346 (30)	466 (27)	1987 (31)	893 (31)
Moderately high	2782 (25)	521 (30)	1625 (25)	636 (22)
Highest	2188 (20)	419 (24)	1287 (20)	482 (17)
High Deductible Insurance, n(%)	454 (4)	69 (4)	248 (4)	137 (5)
Comorbidities				
Smoking, n(%)	2074 (19)	413 (24)	1231 (19)	430 (15)
Alcohol Overuse, n(%)	525 (5)	83 (5)	296 (5)	146 (5)
Depression, n(%)	3333 (30)	573 (33)	1939 (30)	821 (29)
COPD, n(%)	3768 (34)	699 (40)	2249 (35)	820 (29)
Liver Disease, n(%)	179 (2)	60 (3)	94 (1)	25 (1)
Coronary Heart Disease, n(%)	853 (8)	330 (19)	468 (7)	55 (2)
Renal Disease, n(%)	1398 (13)	612 (35)	700 (11)	86 (3)

*CDC Social Vulnerability Index is reported on a scale of 0-1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest).

Table S4. Sample Characteristics of adult KPGA Members with an Incident COVID-19 Diagnosis, 2020-2021, by Allostatic Load Risk Level, Utilizing Method 2 (6 biomarkers) of Allostatic Load Determination

Sample Characteristics	Total Study Population	Allostatic Load Risk Level		
		High	**Moderate**	**Low**
	n = 11,066	(n = 393)	(n = 6,047)	(n = 4,626)
Demographics				
Race, n(%)				
Black	5578 (50)	231 (59)	3237 (54)	2110 (46)
White	3999 (36)	116 (29)	2020 (33)	1863 (40)
Other	1489 (14)	46 (12)	790 (13)	653 (14)
Gender, n(%)				
Female	6774 (61)	182 (46)	3541 (59)	3051 (66)
Male	4292 (39)	211 (54)	2506 (41)	1575 (34)
Age, mean (SD)	52.19 (14.3)	55.51 (13.4)	53.26 (13.3)	50.50 (15.4)
Median Household Income, n(%)				
50k or less	2802 (25)	139 (35)	1645 (27)	1018 (22)
>50k to 100k	7224 (65)	236 (60)	3904 (65)	3084 (66)
>100k to 150k	898 (8)	15 (4)	431 (7)	452 (10)
>150k	136 (1)	3 (1)	62 (1)	71 (2)
Social Vulnerability Index,* n(%)				
Lowest	2743 (25)	71 (18)	1357 (22)	1315 (28)
Moderately low	3346 (30)	106 (27)	1793 (30)	1447 (31)
Moderately high	2782 (25)	123 (31)	1603 (27)	1056 (23)
Highest	2188 (20)	93 (24)	1288 (21)	807 (18)
High Deductible Insurance, n(%)	454 (4)	20 (5)	239 (4)	195 (4)
Comorbidities				
Smoking, n(%)	2074 (19)	98 (25)	1163 (19)	813 (18)
Alcohol Overuse, n(%)	525 (5)	23 (6)	253 (4)	249 (5)
Depression, n(%)	3333 (30)	139 (35)	1812 (30)	1382 (30)
COPD, n(%)	3768 (34)	144 (37)	2139 (35)	1485 (32)
Liver Disease, n(%)	179 (2)	13 (3)	107 (2)	59 (1)
Coronary Heart Disease, n(%)	853 (8)	92 (23)	549 (9)	212 (5)
Renal Disease, n(%)	1398 (13)	183 (47)	901 (15)	314 (7)

*CDC Social Vulnerability Index is reported on a scale of 0-1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest).

Table S5. Sample Characteristics of adult KPGA Members with an Incident COVID-19 Diagnosis, 2020-2021, by Allostatic Load Risk Level, Utilizing Method 3 (quartiles) of Allostatic Load Determination

Sample Characteristics	Total Study Population	Allostatic Load Risk Level		
		High	**Moderate**	**Low**
	n = 11,066	(n = 2,524)	(n = 7,658)	(n = 884)
Demographics				
Race, n(%)				
Black	5578 (50)	1354 (54)	3803 (50)	421 (48)
White	3999 (36)	825 (33)	2811 (37)	363 (41)
Other	1489 (14)	345 (14)	1044 (13)	100 (11)
Gender, n(%)				
Female	6774 (61)	1880 (74)	4551 (59)	343 (39)
Male	4292 (39)	644 (26)	3107 (41)	541 (61)
Age, mean (SD)	52.19 (14.3)	51.70 (13.0)	52.68 (14.5)	49.33 (15.8)
Median Household Income, n(%)				
50k or less	2802 (25)	767 (30)	1860 (24)	175 (20)
>50k to 100k	7224 (65)	1570 (62)	5047 (66)	607 (69)
>100k to 150k	898 (8)	165 (7)	644 (9)	89 (10)
>150k	136 (1)	21 (1)	102 (1)	13 (1)
Social Vulnerability Index,* n(%)				
Lowest	2743 (25)	501 (20)	1965 (26)	277 (31)
Moderately low	3346 (30)	714 (28)	2364 (31)	268 (30)
Moderately high	2782 (25)	716 (28)	1874 (24)	192 (22)
Highest	2188 (20)	592 (24)	1449 (19)	147 (17)
High Deductible Insurance, n(%)	454 (4)	107 (4)	309 (4)	38 (4)
Comorbidities				
Smoking, n(%)	2074 (19)	468 (19)	1431 (19)	175 (20)
Alcohol Overuse, n(%)	525 (5)	103 (4)	362 (5)	60 (7)
Depression, n(%)	3333 (30)	861 (34)	2231 (29)	241 (27)
COPD, n(%)	3768 (34)	953 (38)	2566 (34)	249 (28)
Liver Disease, n(%)	179 (2)	45 (2)	121 (2)	13 (1)
Coronary Heart Disease, n(%)	853 (8)	218 (9)	592 (8)	43 (5)
Renal Disease, n(%)	1398 (13)	256 (10)	1034 (14)	108 (12)

*CDC Social Vulnerability Index is reported on a scale of 0-1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest).

Table S6. Odds Ratio Estimations[1] of the Meditation Relationships between Race, Allostatic Load, and COVID-19 Severity, Utilizing Method 2 (6 biomarkers) of AL Determination

Race	Model 1[2]	Model 2[3]	Model 3[4]	Model 4[5]	Model 5[6]	Model 6[7]
Relationship 1: Race and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	1.07 (0.95, 1.19)	**1.48 (1.31, 1.67)**	**1.32 (1.15, 1.50)**	**1.38 (1.21, 1.57)**	**1.39 (1.22, 1.60)**	**1.30 (1.14, 1.49)**
Other	0.71 (0.59, 0.86)	0.97 (0.80, 1.18)	0.93 (0.76, 1.13)	1.00 (0.82, 1.21)	1.01 (0.83, 1.24)	1.05 (0.86, 1.28)
Relationship 2: Race and Chronic Stress (Models 3-6 use "Low AL Risk" as reference)						
Moderate AL						
White, (ref)			--	--	--	--
Black			**1.42 (1.30, 1.56)**	**1.44 (1.31, 1.57)**	**1.44 (1.31, 1.58)**	**1.56 (1.40, 1.74)**
Other	--	--	**1.16 (1.02, 1.31)**	**1.16 (1.02, 1.32)**	**1.17 (1.03, 1.33)**	**1.20 (1.04, 1.39)**
	1.44 (1.32, 1.56)[8]	**1.62 (1.49, 1.76)[8]**				
High AL	1.11 (0.99, 1.25)[8]	**1.21 (1.07, 1.36)[8]**				
White, (ref)			--	--	--	--
Black			**1.78 (1.39, 2.30)**	**1.89 (1.47, 2.44)**	**1.90 (1.48, 2.45)**	**1.81 (1.55, 2.11)**
Other			1.20 (0.84, 1.72)	1.31 (0.91, 1.89)	1.32 (0.91, 1.90)	1.19 (0.96, 1.47)
Relationship 3: Race, Chronic Stress, and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	0.99 (0.89, 1.11)	**1.37 (1.21, 1.55)**	**1.24 (1.08, 1.41)**	**1.29 (1.13, 1.47)**	**1.31 (1.15, 1.50)**	**1.25 (1.09, 1.43)**
Other	0.69 (0.58, 0.84)	0.96 (0.79, 1.16)	0.92 (0.76, 1.12)	0.99 (0.81, 1.20)	1.00 (0.82, 1.22)	1.04 (0.85, 1.27)

[1] All reported measures are Odds Ratio (95% confidence intervals), using White as the reference group. Bolded estimates are significant.

[2] Model 1 only contains exposure of interest and the mediator, when applicable (Relationship 3)

[3] Model 2 adjusts for gender and age

[4] Model 3 adds CDC SVI, income, and high deductible insurance plan

[5] Model 4 adds smoking status, alcohol use, and depression

[6] Model 4 adds COPD and liver disease

[7] Model 6 adds renal disease and coronary heart disease

[8] Proportional odds assumption met for crude model, so OLR was performed and only one overall AL risk OR reported, representative of the odds of increased AL risk level, across race. Models 2-5 do not meet the assumption, so PLR regression was performed, and thus AL risk strata specific ORs are reported using "Low" allostatic load risk level as the reference group.

Table S7. Odds Ratio Estimations[1] of the Meditation Relationships between Race, Allostatic Load, and COVID-19 Severity, Utilizing Method 3 (quartiles) of AL Determination

Race	Model 1[2]	Model 2[3]	Model 3[4]	Model 4[5]	Model 5[6]	Model 6[7]
Relationship 1: Race and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	1.07 (0.95, 1.19)	**1.48 (1.31, 1.67)**	**1.32 (1.15, 1.50)**	**1.38 (1.21, 1.57)**	**1.39 (1.22, 1.60)**	**1.30 (1.14, 1.49)**
Other	0.71 (0.59, 0.86)	0.97 (0.80, 1.18)	0.93 (0.76, 1.13)	1.00 (0.82, 1.21)	1.01 (0.83, 1.24)	1.05 (0.86, 1.28)
Relationship 2: Race and Chronic Stress (Models 2-6 use "Low AL Risk" as reference)						
Moderate AL						
White, (ref)		--	--	--	--	--
Black		**1.16 (1.00, 1.35)**	1.07 (0.91, 1.26)	1.06 (0.90, 1.25)	1.06 (0.90, 1.25)	1.06 (0.90, 1.25)
Other	--	**1.52 (1.20, 1.93)**	**1.48 (1.16, 1.87)**	**1.44 (1.14, 1.83)**	**1.45 (1.14, 1.85)**	**1.46 (1.15, 1.85)**
	1.23 (1.13, 1.35)					
High AL	**1.21 (1.07, 1.38)**					
White, (ref)		--	--	--	--	--
Black		**1.31 (1.10, 1.55)**	1.07 (0.89, 1.28)	1.08 (0.90, 1.30)	1.08 (0.90, 1.30)	1.10 (0.91, 1.32)
Other		**1.71 (1.32, 2.21)**	**1.56 (1.20, 2.03)**	**1.58 (1.21, 2.06)**	**1.61 (1.23, 2.09)**	**1.62 (1.24, 2.12)**
Relationship 3: Race, Chronic Stress, and COVID-19 Severity						
White, (ref)	--	--	--	--	--	--
Black	1.04 (0.93, 1.17)	**1.47 (1.30, 1.66)**	**1.32 (1.15, 1.50)**	**1.38 (1.20, 1.57)**	**1.40 (1.22, 1.59)**	**1.30 (1.13, 1.48)**
Other	0.70 (0.58, 0.84)	0.95 (0.78, 1.15)	0.91 (0.75, 1.11)	0.98 (0.81, 1.19)	1.00 (0.82, 1.22)	1.03 (0.85, 1.26)

[1] All reported measures are Odds Ratio (95% confidence intervals), using White as the reference group. Bolded estimates are significant.

[2] Model 1 only contains exposure of interest and the mediator, when applicable (Relationship 3)

[3] Model 2 adjusts for gender and age

[4] Model 3 adds CDC SVI, income, and high deductible insurance plan

[5] Model 4 adds smoking status, alcohol use, and depression

[6] Model 4 adds COPD and liver disease

[7] Model 6 adds renal disease and coronary heart disease

[8] Proportional odds assumption met for crude model, so OLR was performed and only one overall AL risk OR reported, representative of the odds of increased AL risk level, across race. Models 2-5 do not meet the assumption, so PLR regression was performed, and thus AL risk strata specific ORs are reported using "Low" allostatic load risk level as the reference group.

Appendix

A. Determination of Blood Pressure Scoring via Medication Uptake

Line list of reported medications was filtered to those prescribed before COVID diagnosis, which consisted of 23,682 participants reporting 79,673 medications. These were then filtered by therapeutic classes, keeping those potentially relevant to blood pressure, including: “antihyperglycemics”, “cardiac drugs”, “cardiovascular”, “diuretics”, “elect/caloric/h2o”, and “unclassified drug products”. The remaining medication prescriptions totaled 30,350. Lastly, these were filtered by pharmaceutical class, keeping those prescribed to regulate blood pressure (37). Final list can be found below. Those reporting any of the listed drugs were categorized as high risk for blood pressure.

1. ACE INHIBITOR-CALCIUM CHANNEL BLOCKER COMBINATION
2. ACE INHIBITOR-THIAZIDE OR THIAZIDE-LIKE DIURETIC
3. ALPHA-ADRENERGIC BLOCKING AGENTS
4. ALPHA/BETA-ADRENERGIC BLOCKING AGENTS
5. ANGIOTEN.RECEPTR ANTAG-CALCIUM CHANL BLKR-THIAZIDE
6. ANGIOTENSIN RECEPTOR ANTAG.-THIAZIDE DIURETIC COMB
7. ANGIOTENSIN RECEPTOR BLOCKR-CALCIUM CHANNEL BLOCKR
8. ANTIHYPERTENSIVES, ACE INHIBITORS
9. ANTIHYPERTENSIVES, ANGIOTENSIN RECEPTOR ANTAGONIST
10. ANTIHYPERTENSIVES, SYMPATHOLYTIC
11. ANTIHYPERTENSIVES, VASODILATORS
12. BETA-ADRENERGIC BLOCKING AGENTS
13. BETA-BLOCKERS AND THIAZIDE,THIAZIDE-LIKE DIURETICS
14. CALCIUM CHANNEL BLOCKING AGENTS
15. LOOP DIURETICS
16. POTASSIUM SPARING DIURETICS
17. POTASSIUM SPARING DIURETICS IN COMBINATION
18. PULM ANTI-HTN,SOLUBLE GUANYLATE CYCLASE STIM

19. PULM.ANTI-HTN,SEL.C-GMP PHOSPHODIESTERASE T5 INHIB
20. PULMONARY ANTI-HTN, ENDOTHELIN RECEPTOR ANTAGONIST
21. THIAZIDE AND RELATED DIURETICS
22. VASODILATORS, COMBINATION

B. Discernment of Smoking History from KPGA EMRs

Diagnosis indicating non-specific tobacco use/smoking or history of non-specific tobacco use/smoking according to ICD-CM codes. First two codes are ICD10; second two codes are ICD9 (58).

1. F17.20%
2. F17.21%
3. 305.1%
4. V15.82

C. Discernment of Alcohol Overuse from KPGA EMRs

Diagnosis indicating toxic alcohol effects, withdrawal, alcohol-related illnesses, problem with alcohol use, and counseling/rehab according to ICD-CM codes. First 10 codes are ICD10; second 10 codes are ICD9 (59).

1. T51.%
2. E52
3. F10.%
4. G62.1%
5. I42.6%
6. K29.2%
7. K70.[039]%
8. Z72.1%
9. Z50.2%
10. Z71.4%
11. 980.%
12. 265.2
13. 291.[1-35-9].%

14. 303.[09]%
15. 305.0%
16. 357.5%
17. 425.5%
18. 535.3%
19. 571.[0-3]%
20. V11.3%